REMARKS

Claims 24-30, 36, 37 and 40 are presented for examination.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

Favorable action on this application is awaited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

The paragraph beginning at page 17, line 8:

Since the method of the subject invention does not make use of the 'active' site of a given target protein, it is able to achieve a level of specificity for a drug molecule previously considered extremely difficult and uncertain using conventional drug discovery efforts. This advantage stems from the constraints placed on existing drug discovery efforts that are based on the need to inhibit an enzyme or receptor binding site that is common to a series of different proteins in different tissues and with very different roles in the physiology of the organism. These [constrains] constraints are based on the common structural elements in the binding or catalytic sites of these related proteins which form the site for conventional drug discovery. The common structural elements typically result in the selection of drugs that will inhibit the whole series of different proteins as these structural elements form the basis for the binding of the drug molecules selected from the screen. Thus conventional drug screening approaches result in the selection of drug hits which do not provide the degree of selectivity desired to bring about a desired therapeutic affect. In the subject invention, since the active site does not need to be the target for the selection of molecules that form the basis of the drug molecule, a significant improvement in the discovery of highly selective drugs is achieved. The consequence is the development of drugs with an enhanced therapeutic value. This advantage is further enhanced by the ability of this drug discovery approach to make use of the whole surface of the given protein target to find molecules with the desired binding specificity. This advantage is then combined with the ability to make use of a rapid screen that is wholly based on the use of binding and thus achieves a level of speed and through put not possible with other methods. This advantage is of great value when the desire is to find a very specific inhibitor of a given member of a protein

family that is highly homologous and thus extremely difficult or impossible for drug discovery based on the effector, receptor or catalytic site of the given protein. This invention thus provides a means for the development of compounds of the invention which are

IN THE CLAIMS

24. (Amended) A method of [modulating] reducing the level and/or activity of [at least one] a target protein in an eukaryotic cell via the [modulation] activation of ubiquitination of said [at least one] target protein comprising contacting said cell with a compound comprising;

c) a ubiquitination recognition element which is able to bind to either the E3 or E2 elements of the ubiquitination system, wherein said ubiquitination recognition element has a molecular weight less than 30,000 and has a binding affinity for said E3 and/or E2 elements of the ubiquitination system of at least 10^2 M^{-1} and;

d) a target protein binding element that is able to bind specifically to [a] said target protein wherein said target protein binding element has a molecular weight of less than 30,000 and has a binding affinity for said target protein greater than 10^5 M^{-1},

wherein said ubiquitination recognition element is covalently linked to said target protein binding element.

25. (Amended) The method of claim 24 where said [at least one target protein is modulated to cause] reduction causes a physiological or metabolic change.

26. (Amended) The method of claim 24 where said [at least one target protein is modulated to cause] reduction causes a pharmacological change.

27. (Amended) The method of claim 24 where said [at least one target protein is modulated to treat] reduction treats a disease.

29. (Amended) The method of claim 28 where said [at least one] target protein is an antigen.

36. (Amended) A method of selectively targeting ubiquitination in a cell comprising contacting said cell with a compound [as in claim 1] comprising:

a ubiquitination recognition element which is able to bind to either the E3 or E2 functional elements of the ubiquitination system, wherein said ubiquitination recognition element has a molecular weight less than 30,000 and has a binding affinity for said E3 and/or E2 elements of the ubiquitination system of at least 10^2 M^{-1} and;

a target protein binding element that is able to bind specifically to a target protein wherein said target protein binding element has a molecular weight of

less than 30,000 and has a binding affinity for said target protein greater than 10^5 M^{-1},

wherein said ubiquitination recognition element is covalently linked to said target protein binding element.